Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 3-8, 13-19, 36, 37, 59, 61-64 and 69-75 are active in the application, with claims 1 and 59 being the independent claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Miscellaneous

In the office action at page 2, the Examiner indicated that "Claim 79 has an additional step of contacting the cells with amyloid as well as adding a substance and determining the effect of the substance on lysosomal dysfunction, microglia activation or changes in cathepsin D content." The claim was withdrawn from consideration because it added the additional step of contacting the cells with amyloid.

Applicants traverse the withdrawal of claim 79. Merely because an additional step was added to the already elected method and a new claim was then presented, this neither places the claim outside the restriction group nor results in the claim being directed to a non-elected invention. As such, Applicants request that the withdrawal of claim 79 be reconsidered and the claim be examined with the rest of the pending claims.

The Examiner addresses the Applicants' attention to MPEP § 821.03. This section of the MPEP states that "[c]laims added by amendment following action by the examiner, . . . to an invention other than previously claimed should be treated as indicated in 37 CFR 1.145." The invention of claim 79 is "not an invention other than

previously claimed," but merely contains a further limitation, i.e. an additional step. Therefore, claim 79 should be examined with the other elected claims.

Rejection Under 35 USC § 132

In the office action at page 2, the examiner objected to the specification under 35 USC § 132 alleging the introduction of new matter. Applicants respectfully traverse this objection.

Specifically, the examiner states that:

> The added material, which is not supported by the original disclosure, is as follows: The originally filed specification clearly states that TGF is a modulator of integrins. The specification states:
>
> > "The term 'condition that modulates integrins or integrin receptors" refers to any condition that might accomplish integrin or integrin receptor modulation. In addition to the compounds referred to in the earlier paragraph, additional examples of modulatory compounds include amyloid beta peptide, oxidative free radicals (OH-, 0_2-, etc.), lysosomal enzyme inhibitors (chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenyl-alanine-diazomethylketone, p-amyloid, and mimetics thereof etc.), or inflammatory factors (TGFβ, IL-1β, LIPS, etc.). These compounds can be used individually or in a cocktail containing a combination of more than one compound or in combination with the above compounds" (specification, page 19, parag. 0065); and
>
> > "Examples of modulatory compounds include oxidative free radicals (Fe, H_20_2, etc.), lysosomal enzyme inhibitors (chloroquine, N-CBZ-L-phenylaianyl-L-alanine-diazomethyketone, N-CBZ-L-phenylaianyl-L-phenylaianine-diazomethylketone, and mimetics thereof etc.), or inflammatory factors (TGFβ, IL-lβ, LPS, etc.)." (specification, page 38, parag. 0123).
>
> Thus, there is no support for applicant's amendment to the specification, which alters the original disclosure such that those compounds originally stated to be modulators of integrins are only compounds to be used with modulators. This alteration presents a material change to the specification, which is not permissible.

Applicants disagree that the amendment to the specification presents a material change to the specification.

In the reply filed on April 23, 2004, Applicants have set forth a reasonable basis for supporting the proposed change to the specification. The Examiner should accept Applicants' statements at face value unless the Examiner can provide objective evidence to the contrary. This, the Examiner has not done.

Rather, the Examiner stated at page 3, last paragraph of the office action that: "In reading paragraph 0065 as originally filed, ***perhaps the artisan would have believed*** applicant had found that the list of compounds in paragraph 0065, previously thought not to modulate integrin or integrin receptor activity, had, by applicant, now been shown to have such activity." (Emphasis added). By speculating on what the artisan "perhaps would have believed" at the time of filing the application, the Examiner has set forth her own opinion of what was known in the art, without documentary or evidentiary support concerning this conclusion. In effect, this is personal knowledge of the Examiner and is not appropriate for use in setting forth a rejection. If the Examiner has such personal knowledge, she is respectfully requested to set forth this information in an Examiner's affidavit as required under 37 CFR 1.104(d)(2). As noted in the MPEP at § 2144.04 (page 2100-138), "If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner ***must*** provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 CFR 1.104(d)(2)." (Emphasis added). In the absence of such an affidavit the objection cannot stand and should be withdrawn.

In the office action at page 3, last paragraph, the Examiner also stated that: "Applicant has not provided evidence that the specification ever contemplated the use of modulatory compounds in conjunction with non-modulatory compounds." Applicants disagree because the following was provided in the reply filed April 16, 2004 as related to a § 102 rejection.

> More specifically, the Examiner stated that: "It is noted to applicant that "condition that modulates integrins or integrin receptors" is disclosed in the specification to include A/β peptide (specification, page 19, parag. 0065, lines 1-4)." This statement appears to be the primary basis for the §102 rejection.
>
> The sentence cited by the Examiner is then followed by: "In addition to the compounds referred to in the earlier paragraph, additional examples of modulatory compounds include amyloid beta peptide, oxidative free radicals . . . β-amyloid . . ." One of skill in the art would readily recognize that the list does not represent compounds that modulate integrin or integrin receptors. Rather, as stated at the end of paragraph 0065, these compounds can be used in combination with the modulatory compounds. Applicants have amended the specification to more clearly state that which is already set forth in paragraph "0065." Support for the changes are found in previous paragraph "0064" that refers to the modulatory compounds and states that "These compounds can be used individually or in a cocktail containing a combination of more than one compound." Paragraph "0065" now more clearly reflects such combinations.

The Examiner has provided no evidence to show that the ordinary artisan would fail to recognize that the list at paragraph 0065 of the specification does not represent compounds that modulate integrin or integrin receptors. Therefore, Applicants reiterate the above basis of support for amending the specification. Based on all of the above, the objection to the specification should be removed.

Rejection Under 35 USC § 112, First Paragraph

In the Office Action at page 4, the Examiner rejected claim 79 under 35 USC § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

Specifically, the examiner could not find support for claim 79 in the specification, and stated that "applicant has not pointed to where such support can be found." Applicant disagrees with the Examiner that claim 79 lack support in the specification.

The Examiner's attention is drawn to the specification at page 46 where it is stated that "cultured hippocampal slices were exposed to media containing the human Aβ-42 sequence in the presence or absence of the integrin antagonist peptide, ..." Thus, the specification supports "exposing brain cells to a condition that modulates integrins or integrin receptors in said cells" and "contacting said cells with amyloid," as required in claim 79. Additional aspects of claim 79 are also supported in the specification at least at pages 46-49. Therefore, the rejection of claim 70 is overcome and should be withdrawn.

Rejection of Claims 1-4, 7, 8, 13, 16-18, 37, 59-61, 63, 64, 69 and 72-74 Under 35 USC § 102.

At page 5, the Examiner maintained the rejection of claims 1-4, 7, 8, 13, 16-18, 37, 59-61, 63, 64, 69 and 72-74 under 35 U.S.C. § 102(b) as being anticipated by Harris-White *et al, The Journal of Neurosci.* 18: 10366-10374 (1998) (hereinafter "Harris-White.") Applicants respectfully traverse this rejection.

Specifically, the Examiner states that:

> Harris-White teaches wild-type rat hippocampal slices as an in vitro model for amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). In particular Harris-White teaches determining the effect of TGFβ on β-amyloid using the hippocampal slice model where the hippocampal slice

> is incubated simultaneously in media comprising both TGFβ and A/β (page 10368, col. 2, parag. 1, lines 1-3). Harris-White teaches that isoforms of TGFβ added to hippocampal slice cultures in conjunction with the addition of Aβ resulted in an increase in the amount of A/β within the slice and a 2 to 3-fold increase of control experiments in the number of plaque-like deposits and prolonged the course of cellular Aβ staining (page 10368, col. 2, parag. 4, lines 5-7 and page 10369, col. 2, parag. 1, lines 22-25). Harris teaches detection of the increase in Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices with antibodies to regions of the Aβ 1-40 polypeptide by both imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5). Thus, Harris-White clearly anticipates the claimed invention.

Applicants disagree that Harris-White anticipates the claimed invention.

In order for cited art to anticipate the claimed invention, each and every limitation of the invention must be found in the cited document. This, has not been shown. As argued in the reply filed April 24, 2004 and reiterated in the current reply, A/β is not a condition that modulates integrins or integrin receptors. Therefore, regardless of Harris-Whites' teachings, the cited art cannot anticipate the claimed invention.

More specifically, at page 6 of the office action, the Examiner sets forth a series of statements to support the contention that Harris-White teaches that A/β "modulates" integrins. The Examiner refers to several alleged observations of Harris-White, however, still fails to point to anything specific where Harris-White actually teaches A/β modulates integrins. Rather, the examiner attempts to reach conclusions from Harris-Whites' mere observations and then argues that this represents a specific teaching. Nowhere in the cited document has Harris-White made such a conclusion. If Applicants have overlooked a conclusion by Harris-White that A/β modulates integrins, they respectfully request that the Examiner points to the specific teaching to support the argument.

Applicants continue to maintain that A/β is not a "condition that modulates integrins or integrin receptors" and that Harris-White's use of either A/β or TGFβ fails to meet at least one of the limitations of the claimed invention. However, even assuming, *arguendo*, that A/β is a condition that modulates integrins or integrin receptors[1], the cited art still fails to anticipate the claimed invention. Applicants' invention as described in claim 1, is a "method for determining the effect of a substance on sequestration, uptake or accumulation of amyloid in brain cells." The method of claim 1, for example, requires several steps in order to practice the invention. The method requires exposing, maintaining, adding and determining various things. Harris-White fails to describe such steps in a "a method for determining the effect of a substance." Regardless of whether the Examiner attempts to point to certain observations of Harris-White concerning the effects of TGFβ, this still fails to describe the method of the claimed invention.

Therefore, for all of the above reasons, this rejection is overcome and should be withdrawn.

Rejection of Claims 1, 2, 5, 6, 36 and 59-62 Under 35 USC § 1003(a).

In the office action at page 6, the Examiner maintained the rejection of claims 1, 2, 5, 6, 36 and 59-62 under 35 U.S.C. § 103 (a) as being unpatentable over Matter *et al.*, *J. Cell Biology 141*:1019-1030 (1998) (hereinafter "Matter") in view of Harris-White. Applicants respectfully traverse this rejection.

Applicants have already argued in the § 102 rejection why Harris-White fails to teach the claimed invention. These same reasons are reiterated in this rejection and therefore, Harris-White even in combination with Matter fails to render obvious the

[1] Applicants, however, do not acknowledge that this is true.

claimed invention. Matter fails to remedy the deficits of Harris-White. Even assuming, *arguendo*, that Matter did remedy the deficits of Harris-White there would still be no motivation or suggestion to combine the teachings of the two documents in an attempt to render obvious the claimed invention.

The Examiner notes that:

> Matter teaches that Integrin α5-negative neuroblastoma cells, IMR-32401, transformed with DNA sequences encoding integrin α5, when incubated with Aβ, resulted in a 5-fold decreased accumulation of Aβ deposits in the cells as compared to non-transformed control cultures (1024, col. 1, parag. 1, lines 4-6).

The examiner also states that "it would have been obvious to the ordinary artisan . . . to perform the analysis of Matter et al using the hippocampal brain slice assay of Harris White . . ." Later, on the same page, the Examiner states that "[t]he substance in Matter is be [sic] the DNA sequence encoding integrin α5." Thus, the Examiner's argument appears to be that DNA for a transformation can be added to Harris-White's tissue slice in an attempt to render obvious Applicants' invention. Applicants disagree.

Regardless of the results obtained by Matter, the cited art still fails to render the claimed invention obvious in view of Harris-White. It is not exactly clear to Applicants exactly how the teachings of Matter and Harris-White are to be combined. However, the Examiner appears to assume that Applicants' invention would be rendered obvious by transforming cells in a tissue slice with the DNA sequence of integrin α5 as done in Matter and then one performs the brain slice assay of Harris-White on the slice with transformed cells. Such an argument would fail for at least two reasons.

First, nowhere in either Matter or Harris-White is there any motivation to combine the cited art. The examiner argues that such motivation exists because the

"hippocampal slice model permits conditions ***most similar*** to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14." (Emphasis added).

Applicants have been unable to find support for this statement in the cited portion of the document. Harris-White does state that, "It is advantageous to find a culture model that will allow for conditions ***most similar*** to the *in vivo* situation and will allow for a longer time course for the development of neurotoxicity." This is clearly ***not*** the same as stating that the hippocampal slice model is ***most similar*** to the *in vivo* situation[2]. Further, there is nothing else in Harris-White that supports the contention that Harris-White's model is ***most*** similar to the *in vivo* situation. Therefore, the Examiner's stated motivation for combining the cited art is not actually present in Harris-White.

Second, nowhere has the Examiner established that 1) one can readily transform cells with DNA in a tissue slice culture similar to what Matter did in cell culture or 2) even assuming that such a transformation could be done, that the transformed cells would be viable for a sufficiently long period of time to practice Applicants' claimed methods. If the examiner is aware of publications showing that one of skill in the art could routinely transform and maintain such transformed cells in a tissue slice for significant periods of time, Applicants respectfully request the Examiner to provide such citations. It should be noted that even if the Examiner may find one or two references to such a procedure, this would hardly make it a routine procedure. Based on the above, it

[2] Applicants note for the record that they also have used a hippocampal slice culture and such cultures represent an *in vitro* model for neurodegenerative diseases. Such tissue slice models may actually be better than cells in culture and may also be the most similar to *in vivo* models, however, Harris-White does not indicate this to be the case and thereby provides no motivation to combine the cited art.

is unlikely that there would be a reasonable expectation of success in obtaining the claimed invention by combining Matter with Harris-White. Therefore, this rejection of the claims under § 103 is overcome and should be withdrawn.

Rejection of Claims 1, 13-15, 59 and 69-71 Under 35 USC § 103(a).

At page 8 of the office action, the Examiner maintained the rejection of claims 1, 13-15, 59 and 69-71 under 35 U.S.C. § 103(a) as being unpatentable over Matter in view of Harris-White. Applicants respectfully traverse this rejection.

Applicants have already argued above in the § 102 and § 103 rejection why Harris-White fails to teach or suggest the claimed invention. For these same reasons which are reiterated in this rejection, Harris-White even in combination with Matter still fails to render obvious the invention of claims 1, 13-15, 59 and 69-71. Matter fails to remedy deficits in Harris-White. Even assuming, *arguendo*, that Matter did remedy the deficits of Harris-White there would still be no motivation or suggestion to combine the teachings of the two documents in an attempt to render obvious the claimed invention.

More specifically, the Examiner states that:

> Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the antibody and peptide studies described in Matter using the hippocampal brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Applicants disagree.

The Examiner again relies on an argument that the brain slice model of Harris-White is presumably more reflective of the *in vivo* situation than cultured cells. As argued above, no such teaching or conclusion was shown to have been actually reached

in Harris-White. If there is no motivation to combine the cited art the rejection is overcome and should be withdrawn.

Additionally, at page 21 of the reply filed April 24, 2004, Applicants provided the following argument concerning the rejection.

> At best, Matter teaches no more than the observation that Aβ when added to cultures affects the amyloid matrix in cells. (pages 1023-1024). According to Matter, the addition of an amyloid antibody decreases formation of such a matrix. This is not the same as "exposing brain cells to a condition that modulates integrins." Regardless of whether Matter allegedly teaches adding an amyloid antibody to a culture or that GRGDSP inhibited Aβ binding to the cell (page 1023, col. 1, parag. 1, lines 23-33), this still fails to disclose Applicants' method. The Examiner may not take disparate independent observations from different pieces of cited art, in an attempt to mix and match and thereby ultimately arrive at Applicants' claimed invention.

The Examiner has indicated in the most recent office action that the above arguments were not persuasive, no reasoning was provided behind Applicants arguments and that Applicants have failed to explain why Matter and Harris-White are disparate observations. The purpose of the above was to demonstrate deficiencies in Matter which precluded that publication from rendering obvious the claimed invention even upon combination with Harris-White. It is still Applicants' position that Matter fails to teach or suggest a condition that modulates integrins. Because Matter fails to do so and Harris-White fails to remedy this shortcoming, the combined art fails to render obvious Applicants' invention. Additionally, the observations from Matter and Harris-White are disparate observations because they are from different and unrelated methods regardless of whether both discuss integrins. The examiner has attempted to take individual steps from totally different methods out of context of the publication as a whole and then inappropriately combine them in order to obtain the claimed invention.

Based on all of the above, the rejection is overcome and should be withdrawn.

Rejection of Claims 1, 19, 59 and 75 Under 35 USC § 103(a)

In the office action at page 9, the Examiner rejected claims 1, 19, 59 and 75 under 35 U.S.C. 103(a) as being unpatentable over Hass *et al., J. Biol. Chem. 273*:13892-13897 (1998) (hereinafter "Hass") in view of Harris-White. Applicants respectfully traverse this rejection.

More specifically, the Examiner states that:

> Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the apoE studies described in Hass using the hippocampal brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Applicants disagree.

The Examiner has set forth an argument concerning why there would be motivation to combine Harris-Whit with Hass that is based on the observation that both publications report results relating to APP and Aβ. Regardless, the Examiner has still failed to address the serious shortcoming of Hass as provided in Applicants' argument presented in the reply of April 24, 2004. The Examiner cannot ignore the fact that Hass describes results with a cell line completely unrelated to brain cells, i.e. African Green Monkey ***kidney*** cells.

Applicants fail to understand how observations in an African Green Monkey ***kidney*** cell line suggest combination with art describing results obtained in a slice of brain. First, the Examiner is comparing cells from two completely different organs, i.e. kidney and brain. Second, the Examiner is most likely comparing cells with minimally differentiated characteristics, i.e. a cell line, with the presumably highly differentiated

cells in a tissue slice. The differences between the two systems are great and therefore, the relationship of results from one system would be suspect as related to the other.

There is no basis for combining the cited and even if combined there would not be a reasonable expectation of success in obtaining the claimed invention.

Applicants have already argued above in the § 102 and § 103 rejection why Harris-White fails to teach or suggest the claimed invention. For the same reasons which are reiterated in this rejection, Harris-White even in combination with Hass fails to render obvious the invention of claims 1, 19, 59 and 75. Hass fails to remedy the deficits of Harris-White. Even assuming, *arguendo*, that Hass did remedy the deficits of Harris-White there would still be no motivation or suggestion to combine the teachings of the two documents in an attempt to render obvious the claimed invention.

The Examiner again relies on an argument that the brain slice model of Harris-White is presumably more reflective of the *in vivo* situation than cultured cells. As argued above, no such teaching or conclusion was actually reached in Harris-White. If there is no motivation to combine the cited art and the rejection is overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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